Biomedical Science

Human T-Lymphotropic Virus Types I and II

JOSEPH D. ROSENBLATT, MD, *Los Angeles, California*

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Human T-lymphotropic virus types I (HTLV-I) and II (HTLV-II) are members of a family of four known retroviruses that are oncogenic as opposed to cytopathic. This family includes HTLV-I and -II, bovine leukemia virus, and simian T-cell leukemia virus. The two types of HTLV are closely related, and for more than a decade we have been aware of the presence of these viruses in humans. In the first part of this article I summarize recent epidemiologic and clinical findings related to the presence of HTLV-I and -II in the Americas. In the second part, I discuss how these viruses may regulate themselves and how in turn they might cause leukemia and neurologic disease in humans.

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Adult T-cell leukemia or lymphoma (ATL) (Figure 1) was the first human malignant neoplasm linked directly to a retrovirus, human T-lymphotropic virus type I (HTLV-I), by the discoveries of Poiesz, Gallo, and Yoshida. The epidemiologic and molecular association of HTLV-I with ATL is clear. In addition to ATL, this unique virus is associated with a slow neurologic disease, formerly known as tropical spastic paraparesis and now known as HTLV-I–associated myelopathy. Virtually all persons with ATL have antibodies to HTLV-I. The virus can transform T lymphocytes in vitro, suggesting that it may play an initiating role in tumor formation in vivo. This virus does not carry a transduced human oncogene and, in fact, does not integrate adjacent to particular human oncogenes with any precision. In different forms of leukemia the site of HTLV-I integration is random, but within a given patient the site of integration of this retrovirus is unique. This tells us that the malignant process arises from a single virally infected cell but that the cell has undergone changes related directly and indirectly to viral infection that render the cell malignant.

In the case of HTLV-associated myelopathy, epidemiologic findings are the primary evidence for viral involvement. Virtually all persons in endemic areas who have a characteristic chronic spastic paralysis, affecting primarily the lower extremities but also resulting in sphincter incontinence, have antibodies to HTLV-I. The virus has been isolated from both the blood and cerebrospinal fluid of these patients. I have studied a familial cluster of this virus in a Mashadi Iranian family in Israel. Several members of the family were infected with HTLV-I, resulting in leukemia in one person and, in another branch of the family, three members in whom HTLV-associated myelopathy developed. This type of familial clustering tells us that either the virus is different or the familial response to this virus may have predisposed certain persons to the development of complications of viral infection. Perhaps 95% of infected persons, however, will have no known clinical consequences.

Recent evidence indicates that human T-lymphotropic virus type II (HTLV-II) may also cause a neurologic disease with symptoms similar to those of HTLV-associated myelopathy. I recently saw a 54-year-old man who was bisexual and had a history of intravenous drug use. He had a 20-year history of progressive leg weakness, initially presenting as paresthesias, that progressed to severe weakness, urinary incontinence, and finally paraparesis that confined him to a wheelchair. On physical examination he had marked spastic weakness of both lower extremities. He had 3+ knee jerks bilaterally and pronounced clonus, as well as a bilateral Babin-

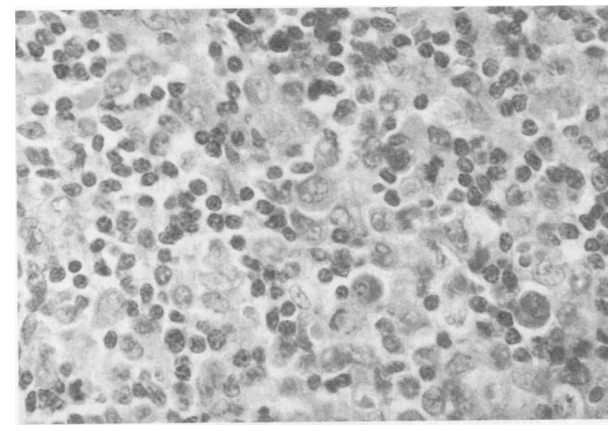

Figure 1.—The photomicrograph was taken of a lymph node from a Japanese patient with adult T-cell leukemia or lymphoma associated with human T-lymphotropic virus type I (hematoxylin-eosin stain) (courtesy of Dr Masao Tomanaga, Atomic Disease Institute, Nagasaki, Japan).

From the AIDS Institute, Division of Hematology-Oncology, Department of Medicine, University of California, Los Angeles, School of Medicine.

Reprint requests to Joseph D. Rosenblatt, MD, Division of Hematology-Oncology, Department of Medicine, UCLA School of Medicine, Center for the Health Sciences, 10833 Le Conte Ave, Los Angeles, CA 90024-1678.

ABBREVIATIONS USED IN TEXT

ATL = adult T-cell leukemia or lymphoma
CAT = chloramphenicol acetyltransferase
HIV-1 = human immunodeficiency virus type 1
HTLV-I, -II = human T-lymphotropic virus type I, II
mRNA = messenger RNA
PTHrP = parathyroid hormone-related protein promoter

ski's reflex. Other findings were consistent with but not diagnostic of HTLV-associated myelopathy, including mild lymphocytosis of the cerebrospinal fluid. Similar to persons with multiple sclerosis, this patient had oligoclonal banding of antibodies in the cerebrospinal fluid. In the case of this particular patient, HTLV-II rather than HTLV-I was identified in his peripheral blood lymphocytes using a polymerase chain reaction on four separate occasions. This is apparently an index case. A similar case was reported in Florida and two other cases were reported in New Mexico in which persons infected with HTLV-II had a paralytic illness similar to this disorder. The patients reported from New Mexico also had cerebral and cerebellar atrophy in one case and cerebellar ataxia thought to be due to infection with HTLV-II. Thus, HTLV-I and -II apparently elicit similar neurologic sequelae in predisposed persons.

In the case of HTLV-II, the less well-known member of this viral family, most people known to be infected are asymptomatic carriers, although some will have a mild T-cell lymphocytosis. Some users of injection drugs who are infected with HTLV-II have had elevated creatine kinase levels, apparently of muscle origin. Four cases of lymphoid malignancy have been linked to HTLV-II, and this appears to be a rare complication of the virus. As opposed to HTLV-I, HTLV-II appears to preferentially infect $CD8^+$ cells; malignant tumors linked to HTLV-II generally have been of the $CD8^+$ T-suppressor cell phenotype, whereas ATL due to HTLV-I almost always involves $CD4^+$ T-helper cells.

Clinical consequences of HTLV-I infection in addition to HTLV-associated myelopathy and ATL have been reported anecdotally. These include polymyositis with or without associated myelopathy, uveitis, and HTLV-I–associated arthropathy, frequently occurring in association with myelopathy. In addition, a growing number of cases have been observed in Jamaica of a pediatric illness, currently designated as "infectious dermatitis," that is associated with recurrent skin infection with staphylococcal and streptococcal bacteria; these cases appear to correlate with HTLV-I seropositivity. The role of HTLV-I in these disorders is poorly understood. A summary of known and suspected sequelae of HTLV-I and -II infection is presented in Table 1.

Since 1985, blood banks in the United States have been screening the blood supply for the prevalence of HTLV-I and -II. In a recent study by Lee and colleagues that looked at almost 500,000 blood donors across the United States in geographically disparate areas, the overall seroprevalence of infection with HTLV-I and -II was estimated to be 0.04%. With the use of discriminatory DNA amplification techniques, 34 of 65 persons (53%) seropositive by serologic reagents derived from HTLV-I were actually infected with HTLV-II. This is surprising because this is one of the few examples in which testing for antibodies using the proteins of one virus, HTLV-I, identifies a large proportion of patients who were actually infected with a related virus, HTLV-II. This is due to the homology between the antigenic proteins of these two viruses. The transmembrane protein P21e is highly antigenic and has a high degree of homology in both viruses. The envelope protein also has a high degree of homology but is somewhat less antigenic; the structural Gag proteins p24 and p19 are highly antigenic and have extensive homology. In the United States, cases of HTLV-II infection are generally associated with intravenous drug use, except in specific ethnic groups (discussed later). In contrast, most persons infected with HTLV-I come from known endemic areas or have had sexual contact with persons from endemic areas. In Lee and associates' study, the vast majority of people interviewed who gave a history of either intravenous drug use or a sexual partner who engaged in intravenous drug use were infected with HTLV-II. Other studies indicate that most seropositive American injection drug users are infected with HTLV-II.

TABLE 1.—*Clinical Manifestations of Infection With Human T-Lymphotropic Virus Type I (HTLV-I) and Type II (HTLV-II)*

HTLV-I
Adult T-cell leukemia or lymphoma (ATL)
Pre-ATL or asymptomatic lymphocytosis
Chronic ATL
Smoldering ATL
Acute-type ATL
HTLV-I–associated myelopathy
HTLV-I–associated arthropathy
Uveitis
Polymyositis?
Sjögren-like syndrome?
Infectious dermatitis in children
Alveolitis or pulmonary disorders?
HTLV-II
$CD8^+$ T-suppressor cell lymphocytosis or leukemia
"Atypical" hairy cell leukemia?
Myositis or abnormal creatine kinase levels
HTLV-II–associated neurodegenerative diseases
Spastic paraparesis
Cerebellar or cerebral atrophy?

Known endemic groups for HTLV-II infection include the Guaymian Indians in Panama, with a 5% to 10% rate of infection, and New Mexico American Indians, in whom a 3% rate of infection was found. Higher rates of HTLV-II infection have also been reported in the Kayapo Indians in Amazonia, Brazil. An interesting report suggests that spider monkeys and capuchin monkeys from South and Central America may be infected with

HTLV-II. Although most Africans and African primates are infected with HTLV-I, Indian populations in the western hemisphere may have been exposed primarily to HTLV-II. The reason for this unusual geographic separation of two closely related viruses is unclear.

An unusual feature of HTLV-I and -II biology relates to the relatively high degree of conservation between different HTLV-I isolates. This is especially striking in contrast to the known variability of isolates of human immunodeficiency virus type 1 (HIV-1). The env sequences from numerous HTLV-I isolates from various areas of Melanesia, Japan, Iran, the Caribbean, and Africa have been compared by Gessain and others. These studies indicate that African and Japanese isolates may be as much as 97% to 99% conserved, whereas Melanesian HTLV-I sequences obtained from geographically isolated tribes in New Guinea may differ by as much as 7% to 8% in the env region from prototypic Japanese isolates. Human T-lymphotropic virus type II may also exist in two closely related subtypes, as defined by consistent differences in restriction maps between isolates. The two original HTLV-II isolates, HTLV-II Mo and HTLV-II NRA, initially characterized by Chen, each correspond to a different subtype, now designated HTLV-II_A and HTLV-II_B, as defined by a study of numerous HTLV-II isolates. The overall degree of genetic heterogeneity between HTLV-II subtypes is not known. Nevertheless, compared with HIV-1, the degree of sequence conservation among HTLV-I and HTLV-II isolates is striking and may reflect lower levels of viral replication or perhaps a different replication strategy.

Pathogenesis and Molecular Biology of HTLV-I and -II

The unique regulatory properties of HTLV-I and -II provide clues to their pathogenesis. The genomic organization and regulatory proteins of HTLV-I and -II are remarkably similar. These viruses, which do not contain an oncogene, are unique in that the 3′ end of their genome contains sizable open reading frames that encode at least two proteins (Figure 2). One is a transcriptional regulator called Tax; the other is a posttranscriptional regulator called Rex that actually regulates the use and transport of viral messenger RNA (mRNA). Both may play a role in pathogenesis and in the viral life cycle. Recently investigators have obtained evidence that additional proteins may also be encoded by the 3′ end of the genome through alternative splice sites, although these are as yet poorly understood, and their role, if any, in the viral life cycle is still unknown.

The Tax protein is a nuclear phosphoprotein that is responsible for enhanced viral RNA transcription from the viral promoter, and HTLV-I and -II will not replicate without Tax. The viral requirement for Tax was first pointed out by Chen, who noted that HTLV-II proviral mutants in Tax made little mRNA. Much evidence suggests that Tax does not limit its effects as a *trans*-activator to viral genes but can actually *trans*-activate a variety of cellular genes. This may be an important clue to pathogenesis by the HTLV viruses. If the viral promoter for HTLV-II, the long terminal repeat, is linked to a bacterial indicator gene such as chloramphenicol acetyltransferase (CAT), expression from that promoter in mammalian cells depends on two processes. First, RNA must be transcribed, and measurable RNA transcription occurs from the viral long terminal repeat only in the presence of Tax. In addition to transcription, expression of the indicator CAT protein is also dependent on the presence of the posttranscriptional regulator, Rex. Although RNA is abundant, its expression is low in the absence of Rex because of the role Rex plays in viral mRNA processing. It appears to facilitate export of full-length gag or pol and partially spliced env mRNA from the nucleus to the cytoplasm.

The early response gene, *egr*-1, is an example of a cellular gene dysregulated by Tax in HTLV-I–infected cells. It is a zinc-finger DNA-binding protein and is thought to be a transcription factor important in early proliferation. Another member of this family of genes is the Wilms' tumor gene. If the promoter of *egr*-1 is linked to a CAT indicator gene, it has been shown that transcription from the *egr*-1 promoter increases substantially, about 20-fold or more by HTLV-I Tax and almost 40-fold by HTLV-II Tax. This may account for a constitutive expression of *egr*-1 in cells infected with HTLV-I and -II.

Another example of cellular gene dysregulation that may actually contribute to the malignant phenotype is that of the parathyroid hormone-related protein promoter (PTHrP), a protein with substantial amino acid homology at its amino terminus to human parathyroid hormone. Cells infected with HTLV-I constitutively express PTHrP, as do ATL cells. In human tumors such as squamous cell carcinoma of the lung, overexpression of this protein may lead to humoral hypercalcemia. Hypercalcemia will develop in more than 70% of persons with ATL. Studies have shown that if the promoter for the PTHrP gene is linked to CAT and studied, it is *trans*-activated

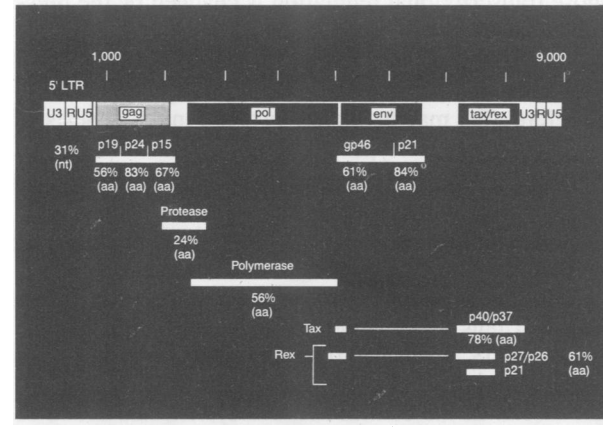

Figure 2.—The diagram shows the genomic organization and nucleic or amino acid homology of the human T-lymphotropic virus types I and II. Known coding regions and protein products for **gag** (structural), **pol** (reverse transcriptase, integrase, ribonuclease H), **env** (envelope), and the transregulatory proteins **tax** and **rex** are indicated beneath a schematic diagram of the complete genome. Nucleic acid homology is indicated by **(nt)**, amino acid homology by **(aa)**.

more than 100-fold by Tax of either HTLV-I or -II. This induction of PTHrP appears to be specific to T cells, as HTLV-infected B-cell lines do not overproduce PTHrP. Hence, Tax effects on the expression of hypercalcemic factors such as PTHrP may account for the hypercalcemia often observed in patients with ATL.

The Tax regulatory protein may also act through a variety of transcriptional pathways to change the phenotype of an infected cell. For example, Tax may increase the expression of the interleukin-2 receptor-α (*IL2R*α) chain genes. Cells infected with ATL and HTLV-I express a high concentration of the high-affinity interleukin-2 receptor on their surface. In this case, Tax *trans*-activates the *IL2R*α chain promoter through inter-

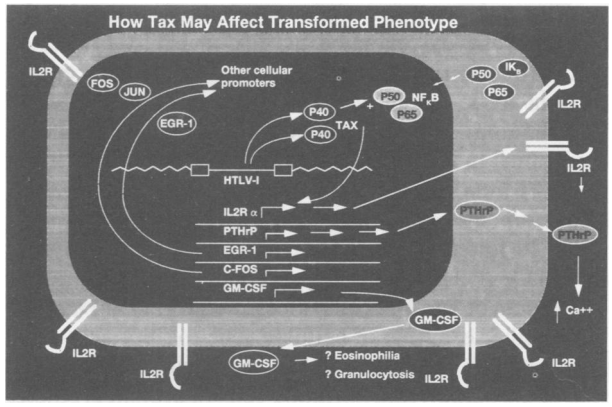

Figure 3.—The effects of Tax on the transformed T-cell phenotype are shown. Cellular genes whose regulation is positively altered by Tax include the *IL2R*α chain of the high-affinity cellular receptor for interleukin-2; parathyroid hormone-related protein promoter **(PTHrP)**, a mediator of humoral hypercalcemia; the cytokine **GM-CSF**; and a variety of transcription factors, including *egr*-1, c-*fos*, and **NF$_x$B**.

action with a transcription factor known as NF-xB. We and others have identified various oncogenes, such as *egr*-1 and c-*fos* and cytokine genes such as *GMCSF*, whose transcriptional regulation is changed by the presence of Tax. Soluble Tax has been shown to possibly enter cells and cause transcriptional effects similar to those seen with the intracellular production of Tax. Therefore, Tax may be highly involved in the genesis of the malignant phenotype. Possible contributions of Tax to the malignant phenotype are outlined in Figure 3. Experiments indicate that Tax, expressed in normal T cells under the control of a herpes Saimiri vector, may be capable of transforming normal T cells. Hence, many investigators think that the myriad cellular effects of Tax may contribute to the pathogenesis of leukemia. In addition, workers at the National Institutes of Health have reported a high frequency of cytotoxic T cells directed against Tax in the central nervous system and blood of patients with HTLV-I–associated myelopathy. Therefore, the immune response to the Tax protein may be involved in the pathogenesis of myelopathy.

We know from epidemiologic studies that infection with HTLV does not generally result in the formation of a malignant neoplasm, and four or five decades may pass following childhood infection before ATL arises. Therefore, secondary events appear to be important in leukemogenesis. These secondary events involve particularly translocations in chromosome 14. Of note, chromosome 14 contains the T-cell receptor α-chain coding sequences. Translocations involving chromosome 14 are often found in ATL cells, but not in carriers of HTLV-I. No characteristic translocation leading to ATL has been identified, however. Perhaps a variety of cytogenetic lesions may lead to the development of ATL in a previously infected cell.

The Rex protein is a posttranscriptional regulator of RNA expression in both HTLV-I and -II and is encoded on the same mRNA as Tax. It occurs in both phosphorylated and nonphosphorylated forms. Work with HTLV-II has shown that Rex is phosphorylated on a serine residue and that only the phosphorylated Rex can bind to viral mRNA target sequences. Genetic studies show that while Tax acts to increase RNA transcription from the viral promoter, Rex acts after RNA has been transcribed to increase expression and, in fact, increases nuclear to cytoplasmic export of that mRNA. Studies have demonstrated a decrease in cytoplasmic viral gag and env mRNA in the absence of Rex. The region through which Rex acts has been mapped to a 225-nucleotide segment downstream from the RNA transcriptional start site in the HTLV-II viral long terminal repeat (Figure 4).

To understand how Rex may mediate its function, Yip studied recombinant Rex produced from a baculovirus expression system and showed that Rex binds specifically and directly to a portion of RNA response element that we had mapped genetically. This can be demonstrated using either a gel retardation or an RNA immunobinding

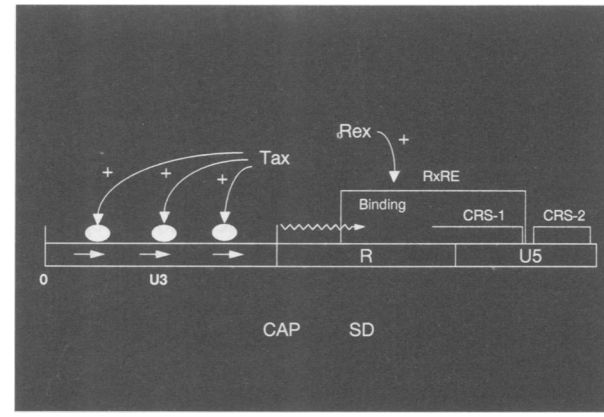

Figure 4.—The proteins Tax, Rex and *cis*-acting elements in the viral long terminal repeat (LTR) regulate the expression of human T-lymphotropic virus types I and II. Tax appears to interact with DNA-binding proteins, which bind to imperfect 21-base pairs repeated enhancer elements in the viral LTR, to increase the rate of transcription **(arrows)**. Rex binds to a *cis*-acting regulatory element, the Rex response element **(RxRE)**, in transcribed messenger RNA (mRNA), and increases the net export of full-length gag or pol mRNA and partially spliced env mRNA. Rex may act to relieve constraints on mRNA export conferred by two *cis*-acting repressive elements (**CRS-1** and **CRS-2**) downstream from the Rex binding element. Of note, the 5′ splice donor site **(SD)** is contained within the Rex binding element. The **CAP** site is the start for viral messenger RNA transcription.

TABLE 2.—*Parallel Evolution of Regulatory Mechanisms in Human Retroviruses*

Human Immunodeficiency Virus Types 1 and 2		*Human T-Lymphotropic Virus Types I and II*	
Regulatory Protein	*Regulatory Mechanism*	*Regulatory Protein*	*Regulatory Mechanism*
Tat	RNA binding	Tax	No direct binding
	Increased messenger RNA (mRNA) transcription		Increased mRNA transcription
	Increased mRNA elongation		Nuclear localization
	Nuclear localization		
Rev	RNA binding	Rex	RNA binding
	Increased gag/env expression		Increased gag/env expression
	Decreased Tat/Rev expression		Decreased Tax/Rex expression
	? Decreased transcription		? Decreased transcription
	Cannot substitute for Rex		Can substitute for Rev
	Nucleolar localization		Nucleolar localization
	Phosphorylated		Phosphorylated form binds RNA
	cis-Acting repressive sequences (CRS) in gag/pol and env mRNA		CRS identified in the long terminal repeat

assay. The RNA migrates normally in the gel, but in the presence of increasing concentrations of Rex more RNA is bound and RNA migration is retarded. The Rex protein binds to its cognate RNA recognition element and requires a specific sequence and RNA secondary structure. We mapped the recognition element and found that, with 100% binding in a wild-type recognition element, specific Rex binding to a 425-base pair transcript from the long terminal repeat can be decreased by more than 90% by altering the Rex binding element by only two nucleotides. Similarly, for Rex to bind efficiently, the splice donor site, which is the site at which RNA is spliced and processed, must also be intact.

Once HTLV-I produces mRNA, the Rex protein can then bind to and alter the fate of that RNA. This may occur as a consequence of Rex binding, following which more unspliced gag or pol mRNA is exported from the nucleus and more virus can be produced. Because splicing occurs at the 5′ splice site and is initiated by binding of an RNA-protein complex called the U1-SnRNP, the fact that Rex may also interact directly with the splice donor site suggests it may interfere directly with the initiation of splicing. Similarly, Rex may relieve the effect of certain negative regulatory sequences in the virus downstream from the sequences that bind Rex. These sequences, called *cis*-acting repressive sequences, are present in both HTLV-I and -II and interact with cellular proteins that govern mRNA exit from nucleus to cytoplasm. Similar regions have been identified in HIV-1. It remains to be determined whether Rex can alter mRNA transport, whether Rex interferes directly with the process of splicing, or whether both mechanisms are affected by Rex.

The Rex protein plays a role in the viral life cycle by altering the use and transport of certain viral RNA. It can actually substitute for an HIV-1 protein called Rev, which has essentially the same function. Rex may affect the splicing, posttranscriptional regulation, or both, of selected cellular mRNA in addition to viral mRNA. Its effects on cellular mRNA, however, are not yet known. A better understanding of the two proteins, Rex and Rev, may provide us with new approaches to treating both HTLV-I and HIV-1 infection.

The two major classes of human retroviruses, HIV (types 1 and 2) and HTLV (types I and II), appear to have independently evolved parallel strategies for replication in the host and for possible evasion of the immune system (Table 2). Both have proteins that increase the overall levels of viral RNA transcription: Tat in the case of HIV-1 and -2 and Tax in the case of HTLV-I and -II. In addition, both have evolved proteins that regulate how the RNA is used and transported in the cell. In the case of HIV, Rev increases expression of the structural and envelope proteins of the virus; this function is performed by Rex in the case of HTLV-I and -II. In addition, both Rev in HIV and Rex in HTLV-I and -II may actually inhibit their own expression and that of the other *trans*-acting regulatory proteins. The comparative study of Tat, Tax, Rev, and Rex has yielded important new insights into the retroviral life cycle and pathogenesis.

These molecular biologic studies are providing an increased understanding of how these viruses may cause dysregulation of the human T cell that leads to the formation of a malignant neoplasm. These studies may also shed light on the development of neurologic diseases as a consequence of HTLV-I and -II infection.

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